Transplanted hESC-Derived Retina Organoid Sheets Differentiate, Integrate, and Improve Visual Function in Retinal Degenerate Rats.

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Authors: Bryce T McLelland, Bin Lin, Anuradha Mathur, Robert B Aramant, Biju B Thomas, Gabriel Nistor, Hans S Keirstead, Magdalene J Seiler

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Funding Grants: Restoring vision by sheet transplants of retinal progenitors and retinal pigment epithelium (RPE) derived from human embryonic stem cells (hESCs)

Public Summary:
Purpose. Age-related macular degeneration (AMD) and retinitis pigmentosa (RP) lead to incurable loss of vision in millions of people. No traditional therapy can restore lost vision in advanced stages of retinal degeneration (RD) due to the irrevocable loss of photoreceptors. The goal of this study was to show that sheets dissected from retinal organoids (mini-retinas developed from human embryonic stem cells (hESCs)) can differentiate, integrate and improve visual function after transplantation to an immunodeficient rat model of severe RD that does not reject human cells. Methods. The gene expression of 3D hESC-retina organoids was analyzed by molecular methods (quantitative polymerase chain reactions) and immunofluorescence. Sheets dissected from retina organoids (30-65d of differentiation) were transplanted into the subretinal space of immunodeficient transgenic rats expressing a mutant photoreceptor protein. These rats have lost most of their photoreceptors at the age of 1 month. Visual acuity was tested by optokinetic testing (OKT). Visual responses to light flashes were recorded from the midbrain (superior colliculus). Transplants were analyzed at 54-300 days post surgery (dps) by immunohistochemistry for donor and retinal markers. Results. Retina organoids contained multiple retinal cell types including progenitor populations capable of developing new cones and rods. After transplantation into an immunodeficient rat model of severe RD, the transplanted sheets differentiated, integrated, and produced functional photoreceptors and other retinal cells, according to the longer human developmental time table. Transplanted RD rats exhibited visual improvements compared to control RD rats as measured by optokinetic testing and electrophysiological recording in the midbrain. Label of the tissue with specific antibodies indicated that the donor cells were synaptically active. Extensive transplant projections could be seen within the host RD retina. Optical coherence tomography (OCT) imaging monitored long term transplant growth and survival up to ten months post-surgery. Conclusions. These data demonstrate that transplantation of sheets dissected from hESC retina organoids is a potential therapeutic method for restoring vision in advanced stages of retinal degeneration.

Scientific Abstract:
Purpose: To investigate whether sheets of retina organoids derived from human embryonic stem cells (hESCs) can differentiate, integrate, and improve visual function in an immunodeficient rat model of severe retinal degeneration (RD). Methods: 3D hESC-derived retina organoids were analyzed by quantitative PCR and immunofluorescence. Sheets dissected from retina organoids (30-65 days of differentiation) were transplanted into the subretinal space of immunodeficient rho S334ter-3 rats. Visual function was tested by optokinetic testing and electrophysiologic recording in the superior colliculus. Transplants were analyzed at 54 to 300 days postsurgery by immunohistochemistry for donor and retinal markers. Results: Retina organoids contained multiple retinal cell types, including progenitor populations capable of developing new cones and rods. After transplantation into an immunodeficient rat model of severe RD, the transplanted sheets differentiated, integrated, and produced functional photoreceptors and other retinal cells, according to the longer human developmental timetable. Maturation of the transplanted retinal cells created visual improvements that were measured by optokinetic testing and electrophysiologic recording in the superior colliculus. Immunohistochemistry analysis indicated that the donor cells were synaptically active. Extensive transplant projections could be seen within the host RD retina. Optical coherence tomography imaging monitored long-term transplant growth and survival up to 10 months postsurgery. Conclusions: These data demonstrate that the transplantation of sheets dissected from hESC-derived retina organoids is a potential therapeutic method for restoring vision in advanced stages of RD.

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